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PAPER

Synthesis of pyrido[2,3-*b*]indoles and pyrimidoindoles *via* Pd-catalyzed amidation and cyclization†

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Biologically and pharmaceutically active core structures containing a new class of 4-hydroxy-α-carbolines, dihydropyrido[2,3-*b*]indoles, pyrimido[4,5-*b*] and [5,4-*b*]indoles have been synthesized in good yields *via* Pd-catalyzed amidation and cyclizations. The keto–enol tautomerism in 4-hydroxy-α-carbolines has been investigated by DFT calculations and spectroscopic techniques. The fluorescence studies of pyrimido[4,5-*b*] and [5,4-*b*]indoles were carried out with good quantum yields.

Introduction

Among the myriad of biologically active heterocycles, nitrogen containing heterocycles[1] play a key role. In fact, recent surveys have reported that a large number of molecules currently under investigation by researchers contain nitrogen heterocycles, and of these, pyrido[2,3-*b*]indoles, pyrimido[4,5-*b*] and [5,4-*b*]-indoles constitute the most important family of compounds. These heterocycles have the common "privileged" indole framework which is commonly found in pharmaceutical drugs and natural products.[2] Therefore, there has been substantial interest in developing efficient methods for the synthesis of these core structures.

Pyrido[2,3-*b*]indoles (α-carbolines) are considered compounds of great interest for their wide range of biological activities, such as antitumor,[3] antiviral,[4] anti-inflammatory,[5] and anxiolytic, and are also useful for the treatment of cancer and immune-related diseases.[6a] These novel biological activities are due to their ability to interact with DNA, which depends on the planarity of the pyrido[2,3-*b*]indole ring system and its functional groups. The core structure of pyrido[2,3-*b*]indole is present in naturally occurring alkaloids (Fig. 1), such as grossularines 1 and 2, dendrodoine A (isolated from *Dendrodoa grossularia*),[3] and mescengricin (isolated from *Streptomyces griseoflavu*),[6b], carcinogenic metabolites and the pyrolysis products from protein foods.[7a,b] In general, the construction of these pyrido[2,3-*b*]-indole core sturctures can be achieved by one of the following processes: (a) cyclization of azaindoles,[7c,d] or (b) annulation of pyridine rings.[7e]

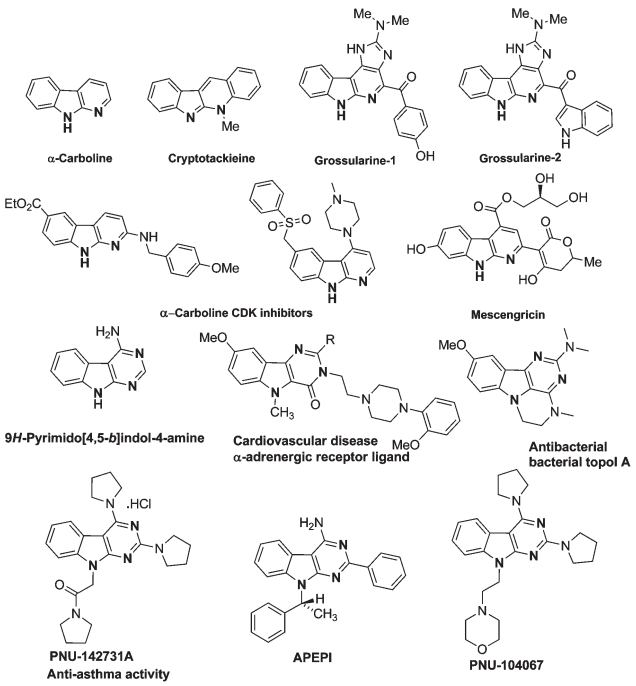

Fig. 1 Biologically and pharmaceutically active pyrido[2,3-*b*]indoles, pyrimido[4,5-*b*] and [5,4-*b*]indoles.

Pyrimido[4,5-*b*] and [5,4-*b*]indole moieties[8] are also prominent structural motifs discerned in numerous pharmaceutically active compounds and show a wide range of significant biological activities, (Fig. 1) such as anti-asthma,[9] antihypertensive and anti-inflammatory,[10] and act as α1-adrenergic receptor ligands or A1 adenosine receptor antagonists,[11] potential tyrosine kinases (PTK) inhibitors, CFR1 and neuropeptide Y receptor ligands.[12a] Pyrimido[4,5-*b*] and [5,4-*b*]indoles are also called 3-aza-α-carbolines and 2-aza-β-carbolines respectively.[12b,c]

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Results and discussion

Due to the ubiquity of these molecular core structures in many biologically and pharmaceutically important molecules, we are exploring the synthetic methods to construct pyrido[2,3-*b*]-indoles, pyrimido[4,5-*b*] and [5,4-*b*]indoles through the Pd-catalyzed amidation reactions of 2-formyl-3-haloindoles and 2-halo-3-carbonylindoles followed by cyclizations. Over the past decade, Pd-catalyzed cross-coupling reactions have emerged as a crucial tool in organic synthesis. Among them, Pd-catalyzed C–N bond formation reactions have great uses in organic synthesis and pharmaceuticals. These reactions, pioneered by the groups of Buchwald and Hartwig,[13] have been extensively studied. On account of an interest in the synthesis of indole fused heterocycles,[14] we first performed amidation at both the 3rd and 2nd positions of 2-formyl-3-haloindoles and 2-halo-3-carbonylindoles.

To obtain the best reaction conditions, we probed the conditions under which the coupling of 1-benzyl-3-chloro-1*H*-indole-2-carbaldehyde, thiophene-2-carboxamide and 3-bromo-1-ethyl-1*H*-indole-2-carbaldehyde with benzamide, for amidation at the 3rd position, proceeded smoothly. We also probed the reaction conditions under which the coupling of 2-bromo-1-ethyl-1*H*-indole-3-carbaldehyde with thiophene-2-carboxamide, for amidation at the 2nd position, proceeded smoothly. We screened various Pd sources, ligands and solvents as shown in Tables S1A and S1B (ESI†).[18] We found that the best reaction conditions for the amidation at the 3rd position of 2-formyl-3-haloindoles involves 1.0 equiv. of 2-formyl-3-chloroindoles or 2-formyl-3-bromoindoles, 1.2 equiv. of amide, 0.75 mol% $Pd_2(dba)_3$, 0.50 mol% BINAP, and 3.0 equiv. of Cs_2CO_3. For the amidation at the 2nd position of 2-halo-3-haloindoles, the best reaction conditions involve 1.0 equiv. of 2-formyl-3-chloroindoles or 2- formyl-3-bromoindoles, 1.2 equiv. of amide, 0.75 mol% $Pd_2(dba)_3$, 0.50 mol% BINAP and 3.0 equiv. of Cs_2CO_3, and for the amidation at the 2nd position of 2-halo-3-carbonylindoles, best conditions involve 0.50 mol% $Pd_2(dba)_3$, 0.25 mol% BINAP, 3.0 equiv. of Cs_2CO_3 and 2.0 mL $mmol^{-1}$ of *t*-BuOH as solvent for the substrates 2-formyl-3-chloroindoles and 2-chloro-3-carbonylindoles whereas toluene is the suitable solvent for 2-formyl-3-bromoindoles and 2-bromo-3-carbonylindoles at 110 °C. By applying these conditions we synthesized various new *N*-(3-carbonyl-1-(substituted)-1*H*-indol-2-yl)amides (**1f–u**) and *N*-(1-(substituted)-2-formyl-1*H*-indol-3-yl)amides (**1a–e**) in good to excellent yields as shown in Table 1. These amide derivatives offer access to various indole fused heterocyclic ring systems. Having established a successful method for the synthesis of various new *N*-(3-acetyl-1-(substituted)-1*H*-indol-2-yl)amides, we proceeded to the base catalyzed Camps[15] cyclization of these amides to yield 2-substituted-pyrido[2,3-*b*]-indol-4(9*H*)-ones.

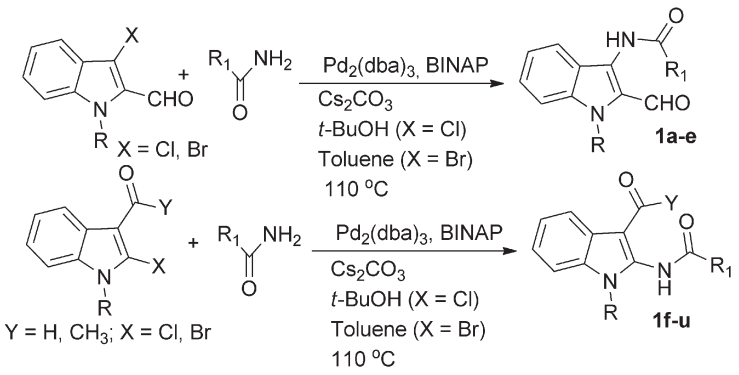
We initiated our investigation for the synthesis of pyrido[2,3-*b*]indol-4(9*H*)-ones with various bases and solvents; the results have been summarized in Table S2A.† The optimal reaction condition for the cyclization of *N*-(3-acetyl-1-(substituted)-1*H*-indol-2-yl)amides to pyrido[2,3-*b*]indol-4(9*H*)-ones was found to involve the use of 5.0 equiv. of *t*-BuOK in THF at 70 °C. This reaction condition proved to be generally applicable to a wide range of *N*-(3-acetyl-1-(substituted)-1*H*-indol-2-yl)amides yielding the corresponding pyrido[2,3-*b*]indol-4(9*H*)-ones. But interestingly, the ^1H and ^{13}C NMR data points towards the formation of 4-hydroxy-α-carbolines rather than the expected pyrido[2,3-*b*]indol-4(9*H*)-ones as the products. We anticipated that the product may be involved in keto–enol tautomerism which was investigated by carrying out various theoretical and spectroscopic studies.

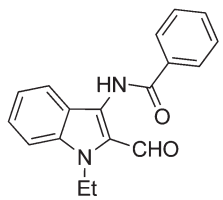
Generally, aliphatic carbonyl compounds which have α-hydrogens undergo keto–enol tautomerism; the keto form is favoured over the enol form due to the stabilization of the carbonyl bond. This general rule is not obeyed by the cyclic conjugated ketone systems; the enol form is predominant over the keto form and the existence of the enol form is supported by the literature[16]. We have proved the existence of enol form by performing spectroscopic studies and electronic structure calculations on the isomers of these molecules.

A density functional theory (DFT) hybrid method with the Becke's 3 parameter exchange functional basis set of Lee, Yang and Parr [(B3LYP) and 6-31+G(D) (valence double zeta plus polarization functions of d type)] was used to optimize the geometries of the two tautomers of the 9-ethyl-2-methyl-1*H*-pyrido-[2,3-*b*]indol-4(9*H*)-one (**2a**). The effect of solvation was also studied here. Three types (gas phase, using MeOH and THF as solvents with polarizable continuum model (PCM) solvent model) of calculations were done on the two tautomers. All the calculations were done using Gaussian 09 package. It is well recognized that this method and basis set are reliable for organic molecules. The two structures converged to a minimum and both minima were verified by establishing that the matrix of energy second derivatives (Hessian) has only positive Eigen values (all vibrational frequencies real). The optimized keto and enol forms are depicted by Fig. S2a and S2b (ESI†).[18] The transition state is verified by the presence of only one large negative vibrational frequency at -1671 cm^{-1}. The obtained transition state is depicted in Fig. S2c.†[18]

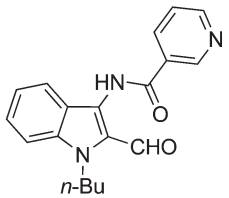
The electronic and activation energies of the two tautomers and transition states in the three models of theory are tabulated in Table 3. From Table 3, it can be seen that the relative energy difference between the enol forms and keto forms is very small. While the enol form is more stable in the gas phase than the keto form by 6.011 kcal mol^{-1}, the keto form is more stable than the enol form by ~3 kcal mol^{-1} in the solvent model. This stabilization can be attributed to the hydrogen bonding of the keto group with methanol. The relative energies are small enough to be in equilibrium with the other counterpart even at room temperature as shown in Table 3. But in our synthesis, the enol form is predominant over the keto form. So, we optimized the transition state for the conversion; the energies are tabulated in Table 3. The activation energies for keto–enol tautomerism are 198.255, 60.774 and 61.342 kcal mol^{-1} in the gas phase and solvent models respectively. These energy barriers cannot be attained at room temperature. So, only one form is predominant. The spectroscopic studies also support this statement. In order to investigate the keto–enol tautomerism, the ^{13}C NMR spectrum of **2f** in DMSO was characterized and we found a group of resonances in the aromatic region and the absence of a carbonyl carbon signal in the δ *ca.* 170.0–210.0 ppm region, which proved that there was no carbonyl carbon in the molecule. This was the first confirmation that the molecule might exist in the

Table 1 Pd-catalyzed cross-coupling of 3-halo-2-formyl indoles, 3-carbonyl-2-haloindoles and amides

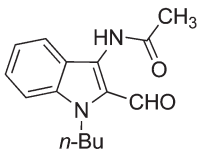




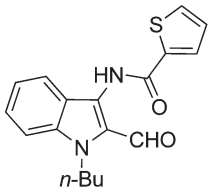
1a
X = Cl 6 h, 79%
X = Br 6 h, 90%



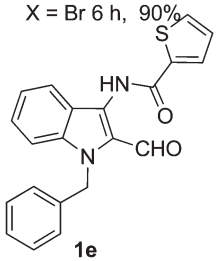
1b
X = Cl 8 h, 81%
X = Br 6 h, 86%



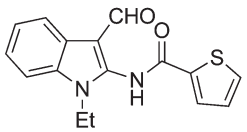
1c
X = Cl 12 h, 78%
X = Br 8 h, 85%



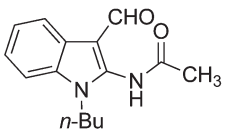
1d
X = Cl 8 h, 85%
X = Br 6 h, 89%



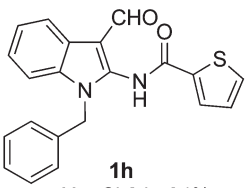
1e
X = Cl 8 h, 92%
X = Br 3 h, 96%



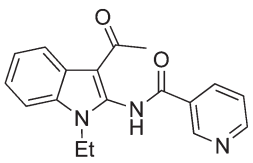
1f
X = Cl 10 h, 87%
X = Br 6 h, 94%



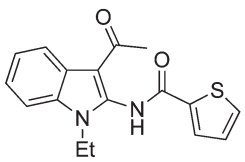
1g
X = Cl 13 h, 85%
X = Br 10 h, 90%



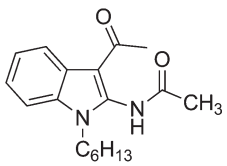
1h
X = Cl 6 h, 94%
X = Br 6 h, 96%



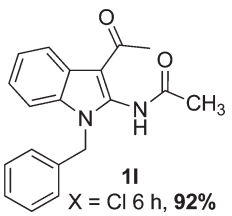
1i
X = Cl 6 h, 82%



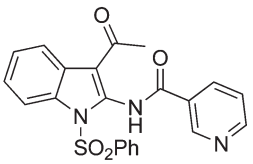
1j
X = Cl 7 h, 80%



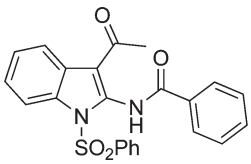
1k
X = Cl 12 h, 79%



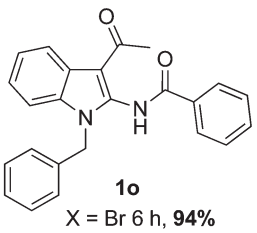
1l
X = Cl 6 h, **92%**



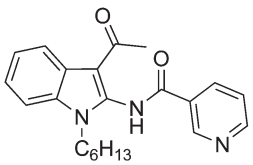
1m
X = Br 6 h, **96%**



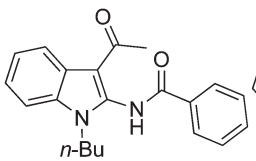
1n
X = Br 6 h, **94%**



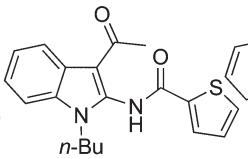
1o
X = Br 6 h, **94%**



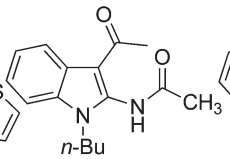
1p
X = Br 6 h, **89%**



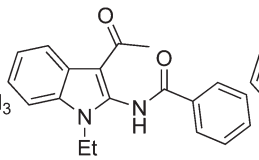
1q
X = Br 6 h, **90%**



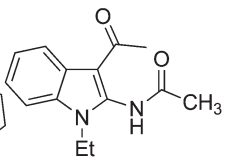
1r
X = Br 8 h, **90%**



1s
X = Br 10 h, **91%**



1t
X = Br 6 h, **94%**



1u
X = Br 10 h, **88%**

enol form rather than the keto form. We recorded a solid state ^{13}C NMR spectrum for the same product and it was further confirmed to exist in the enol form as no carbonyl carbon peak was observed. ^{13}C NMR in the liquid state (DMSO) and solid state are shown in Fig. S3a and S3b (ESI†)[18] respectively. The IR spectrum of the molecule (Fig. S4†)[18] shows a broad peak at $\Delta\nu_{max}$ 3410 cm^{-1}, assigned as an O–H vibration, and does not show a peak for an N–H vibration (~3300 cm^{-1}). If the molecule did exist in the keto form, interactions could be expected between the protons labelled $\mathbf{H_a}$ and $\mathbf{H_b}$ and also between $\mathbf{H_b}$ and $\mathbf{H_c}$ which should result in two cross peaks in the NOESY spectrum. As both these peaks do not appear in the NOESY spectrum (Fig. S3c†), we can assume that these interactions are lacking and that the molecule does not exist in the keto form.

Variable temperature powder X-ray diffraction measurements (Fig. S3d†)[18] also show the same peak pattern at all temperatures measured from −30 °C to 110 °C (mp of **2f** is 122 °C). From these spectra, we concluded that there is no existence of keto–enol tautomerism, and only the enol form exists exclusively at room temperature. Although tautomerism is a difficult subject to study in the gas phase, we recorded the GCMS of **2f** (Fig. S5†),[18] which shows a fragment from the elimination of M-OH (M-17). This indicates the presence of a OH group in **2f**.

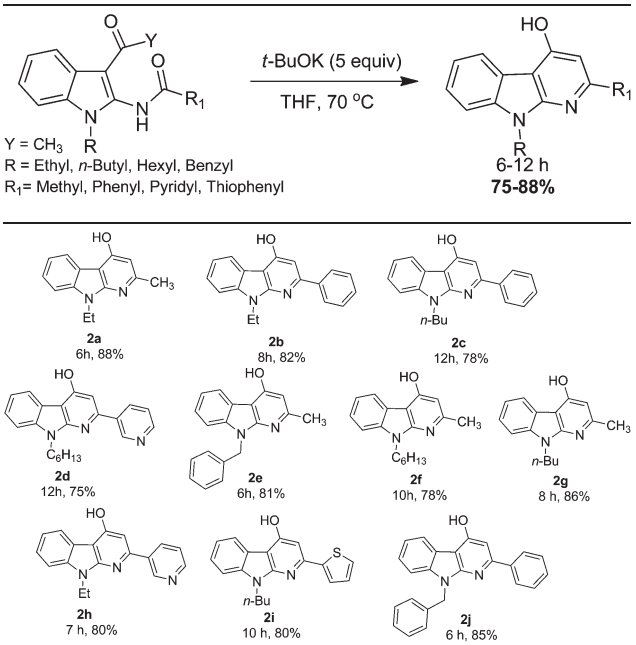
After these spectroscopic confirmations and theoretical calculations, we synthesized various 2-substituted-4-hydroxy-α-carboline (2,9-substituted-9*H*-pyrido[2,3-*b*]indol-4-ol) derivatives **2a–j** successfully by using the above optimized reaction conditions in good yields as shown in Table 2. The work-up of these compounds was particularly facile as, with the exception of **2d**, all the compounds shown in Table 2 could be isolated in pure form without the need to employ column chromatography.

Next we focused on the synthesis of pyrimido[4,5-*b*] and [5,4-*b*]indoles, which can be achieved using one of the following processes: (a) the photochemical reaction of tetrazolopyrimidines,[17a] or (b) intramolecular amination of 4-halo-5-arylpyrimidines.[17b–d] To obtain the best reaction conditions for the synthesis of pyrimido[4,5-*b*] and [5,4-*b*]indoles, we initially tried a one-pot synthesis of highly substituted pyrimidoindoles. Intrigued by these findings, we proceeded to optimize the reaction conditions by using *N*-(3-acetyl-1-butyl-1*H*-indol-2-yl)acetamide (**1s**) as the model substrate. We initiated our investigation with various ammonia sources and solvents as shown in Table S3A†.[18]

To synthesize pyrimido[4,5-*b*] and [5,4-*b*]indoles, we explored two methods (Table 4). **Method A** is a one-pot synthesis, in which we directly added $HCOONH_4$ in *t*-BuOH to the amidation reaction mixture and continued the reaction at 110 °C. **Method B** is a two step synthesis, in which we isolated the amide derivatives **1a–u** during the first step, and in the second step we added $HCOONH_4$ in *t*-BuOH at 110 °C. Of these two methods, **Method B** is superior to **Method A** and using both of these we synthesized **3a–t** in excellent yields (Table 4). The possible mechanisms for the reactions yielding pyrimidoindoles is depicted in Scheme 1. In Scheme 1, $HCOONH_4$ decomposes, probably due to the application of heat, releasing NH_3 which generates the imine which further cyclises in the acid medium due to the presence of excess of $HCOONH_4$. Dehydration, induced by acid and high temperature gives the required pyrimidoindoles (**3a–t**) in good to excellent yields. The work-up of these compounds in **Method B** (step II) was also particularly facile as all the compounds shown in Table 4, could be isolated in pure form without the need to employ column chromatography.

The phenomenon of fluorescence has evolved to be a vital exploratory technique in the various branches of science, importantly, in the areas of analytical, medical and biological sciences *etc*.[19] Among the various classes of organic π-systems, the materials that absorb electromagnetic radiation by intramolecular charge transfer (ICT) and emit from the corresponding photo

Table 2 Base catalyzed Camps cyclization and scope of the reaction substrates[a]

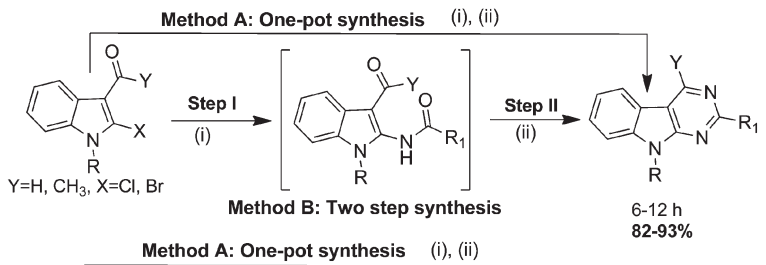


[a] Isolated yields.

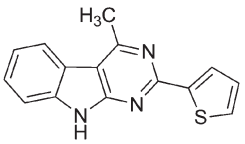
Table 3 The total energy of the keto, enol and transition states at B3LYP/6-31+G(D) level of theory in the gas phase and in solvent

Method	Keto form (Hartree)	Enol form (Hartree)	Transition state energy (Hartree)	Activation energy (kcal mol^{-1})
Gas phase	−726.6992284	−726.7088136	−726.3832852	198.255
MeOH	−726.7225416	−726.7177769	−726.6256917	60.774
THF	−726.8643483	−726.8604681	−726.7665929	61.342

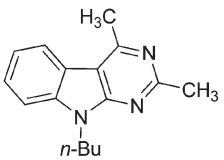
Table 4 Synthesis of pyrimido[4,5-*b*] and [5,4-*b*]indoles and substrate scope[a]



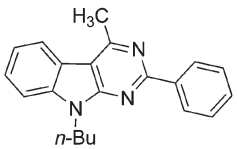
(i) R_1CONH_2, $Pd_2(dba)_3$, BINAP, Cs_2CO_3, *t*-BuOH (X= Cl), Toluene (X= Br), 110 °C; (ii) $HCOONH_4$, *t*-BuOH, 110 °C



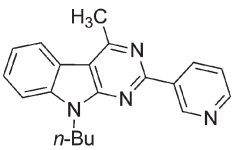
3a
Method A 8 h, **75%**
Method B 6 h, **82%**



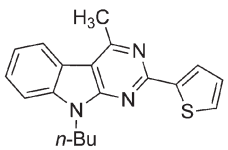
3b
Method A 12 h, **72%**
Method B 10 h, **91%**



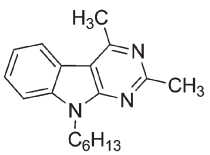
3c
Method A 12 h, **75%**
Method B 10 h, **89%**



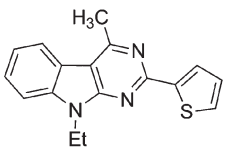
3d
Method A 12 h, **75%**
Method B 10 h, **92%**



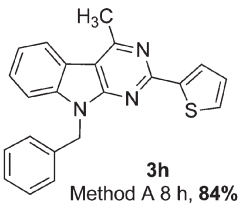
3e
Method A 8 h, **75%**
Method B 6 h, **88%**



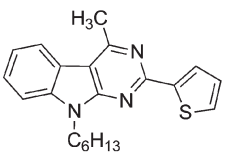
3f
Method B 10 h, **90%**



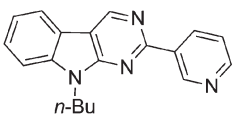
3g
Method B 10 h, **93%**



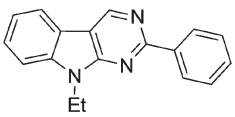
3h
Method A 8 h, **84%**
Method B 6 h, **96%**



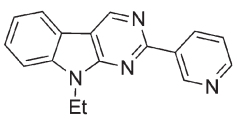
3i
Method A 8 h, **75%**
Method B 6 h, **90%**



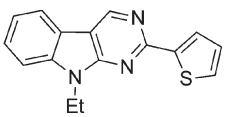
3j
Method B 10 h, **91%**



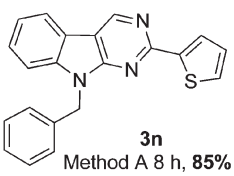
3k
Method B 6 h, **92%**



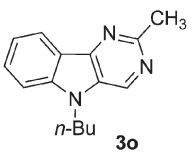
3l
Method B 6 h, **90%**



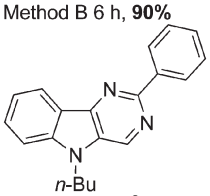
3m
Method A 8 h, **75%**
Method B 6 h, **92%**



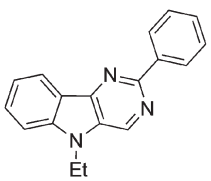
3n
Method A 8 h, **85%**
Method B 6 h, **94%**



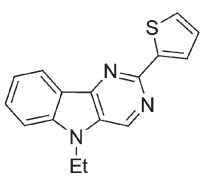
3o
Method A 12 h, **78%**
Method B 6 h, **91%**



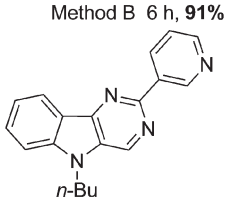
3p
Method A 8 h, **89%**
Method B 6 h, **92%**



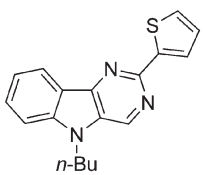
3q
Method A 8 h, **84%**
Method B 6 h, **95%**



3r
Method A 8 h, **89%**
Method B 6 h, **93%**

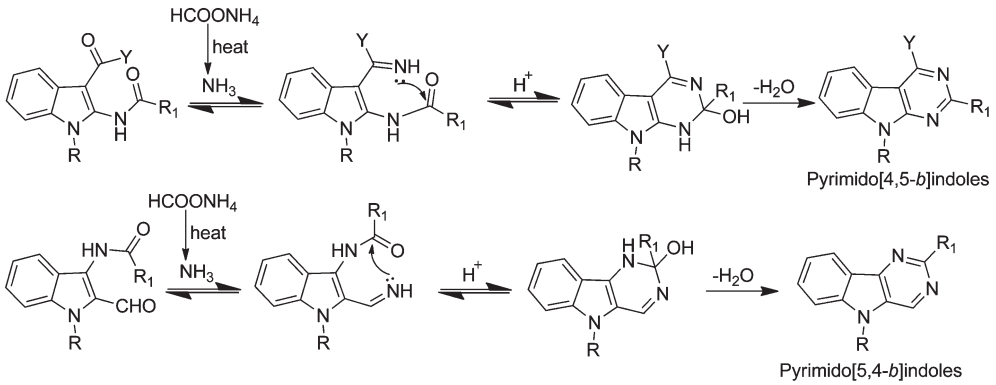


3s
Method A 8 h, **86%**
Method B 6 h, **90%**



3t
Method A 10 h, **89%**
Method B 6 h, **95%**

[a] Isolated yields.



Scheme 1 Possible mechanisms for the reactions yielding pyrimido[4,5-*b*] and [5,4-*b*]indoles.

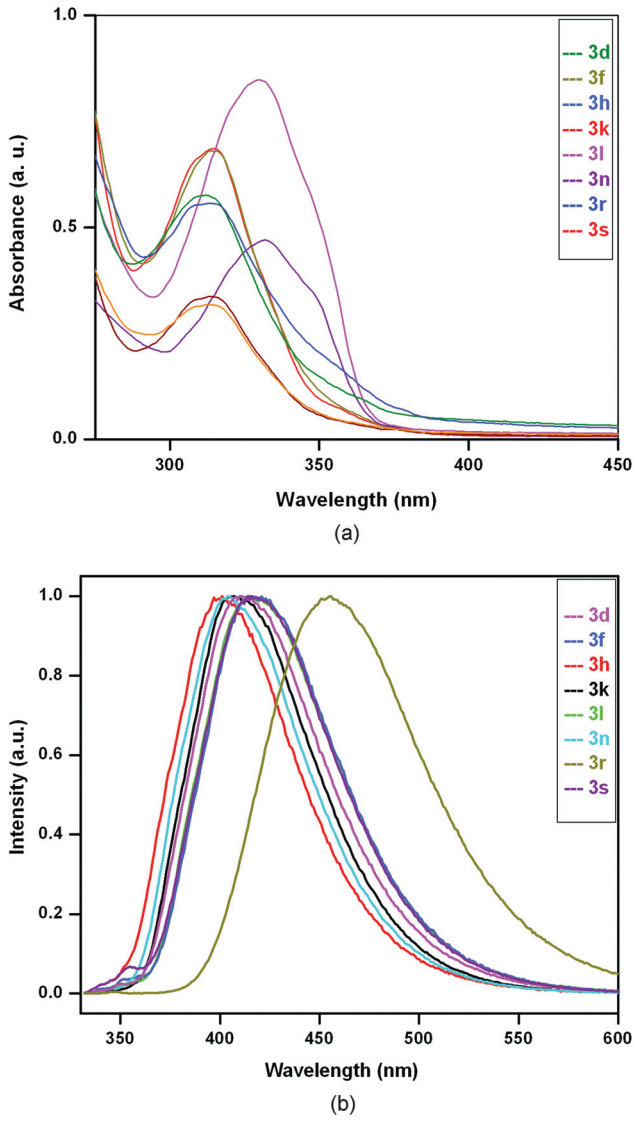


Fig. 2 (a) UV–visible absorption spectra (b) emission spectra of pyrimidoindoles in DCM.

excited state are most fascinating because of their remarkable applications in the field of molecular electronics, integrated photonic devices and non-linear optics,[20] *etc.* Having an interest in the applications of fluorescence studies, we studied the UV-visible and emission spectral properties of pyrimido[4,5-*b*] and [5,4-*b*]indoles (**3d**, **3f**, **3h**, **3k**, **3l**, **3n**, **3p**, **3r**, **3s**) in DCM (10^{-5} mol dm^{-3}) at 300 K. Absorptions and emissions of these pyrimidoindoles are almost identical, as shown in Fig. 2.

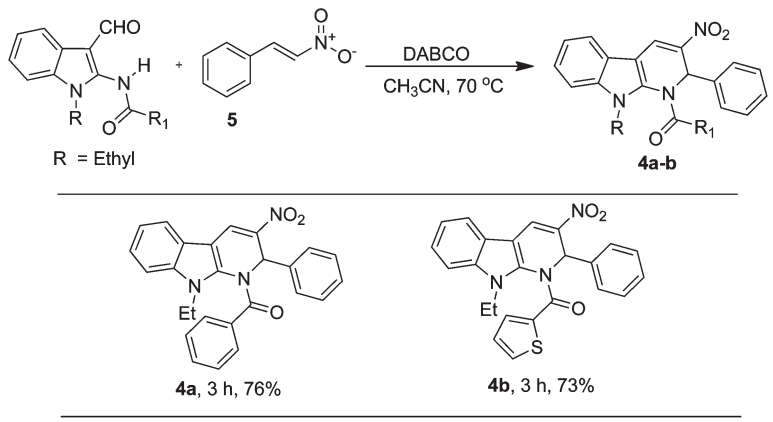
Table 5 Summary of optical data of the synthesized pyrimidoindoles

Compound	λ_{max} (nm)	λ_{em} (nm)	E_{max} (cm^{-1})	Φ_F
3d	311	408	24 509	0.4821
3f	315	417	23 980	0.4924
3k	315	406	24 630	0.4570
3l	330	416	24 038	0.4927
3n	332	404	24 752	0.4439
3p	313	415	24 096	0.4989
3r	314	454	22 026	0.5288
3s	314	416	24 038	0.4946

λ_{max} and E_{max} = absorption and emission maxima respectively.

These pyrimidoindoles show absorption maxima (λ_{max}) in the region of 311–332 nm. The emission spectra of these pyrimidoindoles in DCM (10^{-5} mol dm^{-3}) revealed band maxima in the region of 400–454 nm and the corresponding excitation wavelengths are shown in Fig. 2(b). The emission quantum yields of the compounds **3d**, **3f**, **3h**, **3k**, **3l**, **3n**, **3p**, **3r** and **3s** at room temperature (using quinine sulphate in 1 NM H_2SO_4 as the reference, whose quantum yield is known to be 0.54520) were found to be 0.48, 0.49, 0.45, 0.49, 0.44, 0.49, 0.52, and 0.49 respectively as shown in Table 5. The molecules were excited at the same optical densities where the of the sample intersects the absorption curve of quinine sulphate.

The amide derivatives, such as *N*-(1-ethyl-3-formyl-1*H*-indol-2-yl)benzamide, underwent a Michael reaction with nitro styrene (**5**) in the presence of DABCO/MeCN at 70 °C to furnish the functionalised dihydropyrido[2,3-*b*]indoles (**4a–b**) as shown in Scheme 2. The reaction proceeds through Michael addition of amide derivatives to nitro styrene followed by aldol condensation. We carried out the same reaction using different bases such as triethyl amine, piperidine and sodium ethoxide but observed a faster and cleaner reaction with DABCO. These dihydropyrido[2,3-*b*]indoles (**4a–b**) were confirmed by ^1H and ^{13}C NMR spectra and thoroughly characterized by mass and elemental analysis.



Scheme 2 Synthesis of dihydropyrido[2,3-*b*]indoles.

Conclusions

In summary, we have described a new and efficient synthetic methodology for the construction of biologically and pharmaceutically active core structures containing pyrido[2,3-*b*]indoles, dihydropyrido[2,3-*b*]indoles, pyrido[4,5-*b*] and [5,4-*b*]indoles. A Pd-catalyzed amidation reaction was used for the C–N bond formation at both the 3rd and 2nd positions of indoles using various amide derivatives in good to excellent yields. By using the amide precursors, we have synthesized a diverse range of pyrido[2,3-*b*]indoles, pyrido[4,5-*b*] and [5,4-*b*]indoles under very mild conditions with remarkably high yields. The keto–enol tautomerism in hydroxy-α-carbolines has been investigated by the DFT calculations. Fluorescence studies of pyrido[4,5-*b*] and [5,4-*b*]indoles resulted in good quantum yields.

Experimental section

General information

The procedure does not require an inert atmosphere. All the amide products obtained were purified by column chromatography using silica gel (100–200 mesh). Hexane was used as a co-eluent. ^{1}H and ^{13}C NMR were recorded in 400 and 100 MHz spectrometers respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. IR spectra were recorded on an FT/IR spectrometer. Elemental analyses were recorded on a Flash EA 1112 analyzer in the School of Chemistry, University of Hyderabad. Mass spectra were recorded on either a VG7070H mass spectrometer using the EI technique or a LCMS-2010 mass spectrometer. Melting points were measured in open capillary tubes and are uncorrected.

General procedure for the coupling of 3-haloindole-2-carbaldehye and amide. An oven dried Ace Pressure tube with a Teflon stir bar was charged with $Pd_2(dba)_3$ (if X = Cl, 1.0 mol%, 2.0 mol% Pd, if X = Br, 0.75 mol%, 1.5 mol% Pd), BINAP (0.50 mol%), amide (1.2 equiv.), Cs_2CO_3 (3.0 equiv.), 3-haloindole-2-carbaldehyde (1.0 equiv.) and if X = Br, toluene (1.0 mL) or if X = Cl, *t*-BuOH (2.0 mL) and then capped with a Teflon screw cap and the mixture was heated to 110 °C with stirring according to the mentioned time in Table 1. At this point, the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and the resulting solution was filtered through celite, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate) to give the corresponding coupled product.

General procedure for the coupling of 2-halo-3-carbonylindoles and amide. An oven dried Ace Pressure tube with a Teflon stir bar was charged with $Pd_2(dba)_3$ (0.50 mol%, 1.0 mol% Pd), BINAP (0.25 mol%), amide (1.2 equiv.), Cs_2CO_3 (3.0 equiv.) and 2-halo-3-carbonylindoles (1.0 equiv.) and if X = Br, toluene (2.0 mL) or if X = Cl, *t*-BuOH (2.0 mL) and then capped with a Teflon screw cap and the mixture was heated to 110 °C with stirring according to the mentioned time in Table 1. At this point, the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and the resulting solution was filtered through celite, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate) to give the corresponding coupled product.

General procedure for the coupling of 1-benzyl-3-chloro-1*H*-indole-2-carbaldehyde and thiophene-2-carboxamide. An oven dried Ace Pressure tube with a Teflon stir bar was charged with $Pd_2(dba)_3$ (5.7 mg, 1.85 μmol, 2.0 mol% Pd), BINAP (5.0 mg, 0.92 μmol, 0.5 mol%), thiophene-2-carboxamide (28 mg, 0.07 mmol), base [Cs_2CO_3 (195 mg) or K_3PO_4 (127 mg) or K_2CO_3 (83 mg) or *t*-BuOK (58 mg)], 1-benzyl-3-chloro-1*H*-indole-2-carbaldehyde (0.05 g, 0.185 mmol) and *t*-BuOH (2.0 mL) and then capped with a Teflon screw cap and the mixture was heated to 110 °C with stirring for 8 h. At this point, the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and the resulting solution was filtered through celite, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate) to give the corresponding coupled product (**1e**) as pale yellow solid; m.p. 217–219 °C; IR (KBr): 3259, 3120, 2845, 1763, 1669, 1632, 1529, 1427, 1372, 1209, 1109, 1012, 915, 739 cm^{-1}. ^{1}H NMR (400 MHz, TMS, $CDCl_3$) δ: 10.62 (s, 1H), 10.22 (s, 1H), 7.95 (d, 1H, J = 8.0 Hz),

7.83–7.82 (m, 1H), 7.64–7.63 (m, 1H), 7.33–7.31 (m, 1H), 7.30–7.24 (m, 5H), 7.18–7.15 (m, 1H), 7.09–7.07 (m, 2H), 5.62 (s, 2H). ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ: 185.6, 160.7, 142.3, 137.7, 136.0, 134.9, 134.4, 133.7, 133.1, 132.1, 130.8, 128.9, 128.3, 127.7, 126.8, 125.5, 123.2, 117.8, 111.6, 105.2, 49.4. LC-MS: m/z = 361 (M + H), positive mode; Anal. Calcd for molecular formula $C_{21}H_{16}N_2O_2S$; C, 69.98; H, 4.47; N, 7.77%; found: C, 69.71; H, 4.38; N, 7.67%.

***N*-(1-Butyl-2-formyl-1*H*-indol-3-yl)nicotinamide (1b).** Yellow solid; m.p. 196–198 °C; IR (KBr): 3329, 3222, 2917, 1792, 1662, 1522, 1460, 1329, 1262, 1209, 1111, 917, 725 cm^{-1}. ^{1}H NMR (400 MHz, TMS, $CDCl_3$) δ: 10.79 (s, 1H), 10.02 (s, 1H), 9.30 (s, 1H), 8.76 (s, 1H), 8.35 (d, 1H, J = 8.0 Hz), 7.99–7.97 (m, 1H), 7.39–7.28 (m, 4H), 4.11 (t, 2H, J = 8.0 Hz), 1.81–1.74 (m, 2H), 1.30–1.22 (m, 2H), 0.86 (t, 3H, J = 8.0 Hz). ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ: 184.8, 165.0, 153.0, 149.0, 135.9, 134.5, 132.3, 128.7, 126.9, 125.0, 123.8, 123.4, 123.1, 119.1, 110.8, 44.9, 30.9, 20.1, 13.6. LC-MS: m/z = 322 (M + H), positive mode; Anal. Calcd for molecular formula $C_{19}H_{19}N_3O_2$; C, 71.01; H, 5.96; N, 13.08%; found: C, 71.22; H, 5.89; N, 13.15%.

***N*-(1-Butyl-2-formyl-1*H*-indol-3-yl)acetamide (1c).** Orange solid; m.p. 131–133 °C; IR (KBr): 3317, 3222, 2950, 1795, 1655, 1562, 1498, 1329, 1225, 1209, 1127, 919, 725 cm^{-1}. ^{1}H NMR (400 MHz, TMS, $CDCl_3$) δ: 9.99 (s, 1H), 9.61 (s, 1H), 8.02 (d, 1H, J = 8.0 Hz), 7.33–7.24 (m, 3H), 4.09 (t, 2H, J = 8.0 Hz), 2.28 (s, 3H), 1.79–1.71 (m, 2H), 1.33–1.25 (m, 2H), 0.91 (t, 3H, J = 8.0 Hz). ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ: 184.6, 170.5, 141.6, 134.3, 124.8, 123.8, 123.4, 123.0, 119.3, 110.7, 107.2, 44.4, 30.9, 20.1, 13.6. LC-MS: m/z = 259 (M + H), positive mode; Anal. Calcd for molecular formula $C_{15}H_{18}N_2O_2$; C, 69.74; H, 7.02; N, 10.84%; found: C, 69.81; H, 7.12; N, 10.76%.

General procedure for the coupling of 3-bromo-1-ethyl-1*H*-indole-2-carbaldehyde and benzamide. An oven dried Ace Pressure tube with a Teflon stir bar was charged with $Pd_2(dba)_3$ (1.3 mg, 1.4 μmol, 1.0 mol% Pd), BINAP (0.60 mg, 0.9 μmol, 0.25 mol%), benzamide (28 mg, 0.239 mmol), base [Cs_2CO_3 (195 mg) or K_3PO_4 (127 mg) or K_2CO_3 (83 mg) or *t*-BuOK (58 mg)], 3-bromo-1-ethyl-1*H*-indole-2-carbaldehyde (0.05 g, 0.199 mmol) and toluene (2.0 mL) and then capped with a Teflon screw cap and the mixture was heated to 110 °C with stirring for 8 h. At this point, the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and the resulting solution was filtered through celite, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate) to give the corresponding coupled product (**1a**) as pale brown solid; m.p. 113–115 °C; IR (KBr): 3352, 3217, 2920, 1789, 1653, 1519, 1454, 1390, 1222, 1210, 1109, 918, 727 cm^{-1}. ^{1}H NMR (400 MHz, TMS, $CDCl_3$) δ: 9.87 (s, 1H), 9.62 (s, 1H), 7.94 (d, 2H, J = 8.0 Hz), 7.74 (d, 1H, J = 8.0 Hz), 7.62 (d, 1H, J = 8.0 Hz), 7.47–7.43 (m, 1H), 7.29–7.20 (m, 4H), 3.92 (q, 2H, J = 8.0 Hz), 1.22 (t, 3H, J = 8.0 Hz). ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ: 189.2, 167.8, 136.2, 136.0, 134.8, 132.5, 132.4, 128.6, 127.8, 124.5, 123.0, 121.7, 121.6, 120.6, 110.4, 106.5, 38.2, 14.5. LC-MS: m/z = 293 (M + H), positive mode; Anal. Calcd for molecular formula $C_{18}H_{16}N_2O_2$; C, 73.95; H, 5.52; N, 9.58%; found: C, 73.85; H, 5.51; N, 9.45%.

General procedure for the coupling of 2-bromo-1-ethyl-1*H*-indole-3-carbaldehyde and thiophene-2-carboxamide. An oven dried Ace Pressure tube with a Teflon stir bar was charged with $Pd_2(dba)_3$ (0.9 mg, 0.99 μmol, 1.0 mol% Pd), BINAP (0.31 mg, 0.49 μmol, 0.25 mol%), thiophene-2-carboxamide (30 mg, 0.239 mmol), base [Cs_2CO_3 (195 mg) or K_3PO_4 (127 mg) or K_2CO_3 (83 mg) or *t*-BuOK (58 mg)], 2-bromo-1-ethyl-1*H*-indole-3-carbaldehyde (0.2 g, 5.9 μmol) and *t*-BuOH (2.0 mL) and then capped with a Teflon screw cap and the mixture was heated to 110 °C with stirring for 8 h. At this point, the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and the resulting solution was filtered through celite, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate) to give the corresponding coupled product (**1f**) as pale yellow solid; m.p. 147–149 °C; IR (KBr): 3252, 3159, 2876, 1778, 1669, 1612, 1466, 752, 717 cm^{-1}. ^{1}H NMR (400 MHz, TMS, $CDCl_3$) δ: 10.67 (s, 1H), 10.09 (s, 1H), 7.92–7.91 (m, 2H), 7.61 (d, 1H, J = 8.0 Hz), 7.39–7.37 (m, 1H), 7.31–7.13 (m, 3H), 4.30 (q, 2H, J = 8.0 Hz), 1.46 (t, 3H, J = 8.0 Hz). ^{13}C NMR (100 MHz, TMS, CDCl3) δ: 184.8, 160.8, 141.9, 137.5, 134.4, 134.1, 132.7, 130.9, 128.9, 125.4, 123.1, 123.0, 118.0, 110.8, 40.8, 14.1. LC-MS: m/z = 299 (M + H), positive mode; Anal. Calcd for molecular formula $C_{16}H_{14}N_2O_2S$; C, 64.41; H, 4.73; N, 9.39%; found: C, 64.32; H, 4.79; N, 9.28%.

General procedure for base-promoted cyclization to 2-substituted-4-hydroxy-α-carbolines. An oven dried Ace Pressure tube with a Teflon stir bar was charged with *N*-(3-acetyl-1-(substituted)-1*H*-indol-2-yl)amides (1.0 equiv) and *t*-BuOK (5.0 equiv) in THF (6 mL). The pressure tube was then sealed with a Teflon screw-cap and the reaction was placed in a preheated oil bath at 110 °C. The reaction mixture was stirred according to the mentioned time in Table 2 and then removed from the oil bath and allowed to cool to room temperature. The reaction mixture was then diluted with ethyl acetate. The resultant reaction mixture was extracted with EtOAc (20 mL), washed with water (100 mL) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to obtain the pure product (**3a–3j**). Hexane was added and removed twice more before the product was dried *in vacuo*.

9-Ethyl-2-methyl-9*H*-pyrido[2,3-*b*]indol-4-ol (2a). Pale yellow solid; m.p. 117–119 °C; IR (KBr): 3429, 2927, 1658, 1026, 1003, 769, 725, 570, 528 cm^{-1}. ^{1}H NMR (400 MHz, TMS, DMSO-d_6) δ: 10.88 (s, br, 1H), 7.94 (1H, d, J = 6.16 Hz), 7.54 (d, 1H, J = 8.0 Hz), 7.36–7.33 (m, 1H), 7.20–7.17 (m, 1H), 6.29 (s, 1H), 4.40 (q, 2H, J = 5.68 Hz), 2.68 (s, 3H), 1.29 (t, 3H, J = 5.72 Hz). ^{13}C NMR (100 MHz, TMS, DMSO-d_6) δ: 162.9, 149.5, 145.7, 137.6, 124.0, 121.7, 121.2, 120.0, 109.5, 106.8, 103.3, 36.0, 26.0, 14.3. LC-MS: m/z = 225 (M + H), negative mode; Anal. Calcd for molecular formula $C_{14}H_{14}N_2O$; C, 74.31; H, 6.24; N, 12.38%; found: C, 74.42; H, 6.21; N, 12.28%.

9-Ethyl-2-phenyl-9*H*-pyrido[2,3-*b*]indol-4-ol (2b). Yellowish orange solid; m.p. 152–154 °C; IR (KBr): 3425, 2924, 1635, 1572, 1456, 1379, 1338, 1178, 1109, 1022, 750 cm^{-1}. ^{1}H NMR

(400 MHz, TMS, $CDCl_3$) δ: 11.73 (s, br, 1H), 8.24 (d, 1H, J = 6.0 Hz), 8.11 (d, 2H, J = 6.0 Hz), 7.50–7.40 (m, 4H), 7.39–7.32 (m, 1H), 7.31–7.29 (m, 1H), 7.06 (s, 1H), 4.61 (q, 2H, J = 6.0 Hz); 1.52 (t, 3H, J = 5.6 Hz). ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ: 159.3, 155.3, 153.5, 140.0, 138.6, 128.9, 128.6, 128.5, 128.0, 127.1, 125.2, 122.9, 120.0, 119.7, 108.6, 102.8, 100.3, 36.3, 14.1. LC-MS: m/z = 289 (M + H), positive mode; Anal. Calcd for molecular formula $C_{19}H_{16}N_2O$; C, 79.14; H, 5.59; N, 9.72%; found: C, 79.24; H, 5.51; N, 9.65%.

9-Butyl-2-phenyl-9*H*-pyrido[2,3-*b*]indol-4-ol (2c). Brown solid; m.p. 132–134 °C; IR (KBr): 3431, 2920, 1635, 1568, 1452, 1362, 1330, 1176, 1100, 1025, 756 cm^{-1}. ^{1}H NMR (400 MHz, TMS, DMSO-d_6) δ: 11.63 (s, br, 1H), 8.27 (d, 1H, J = 6.16 Hz), 8.00 (d, 2H, J = 4.0 Hz), 7.47–7.40 (m, 4H), 7.36 (d, 1H, J = 5.6 Hz), 7.31–7.28 (m, 1H), 6.98 (s, 1H), 4.53 (t, 2H, J = 8.0 Hz), 1.91–1.96 (m, 2H), 1.47–1.39 (m, 2H), 0.97 (t, 3H, J = 8.0 Hz). ^{13}C NMR (100 MHz, TMS, DMSO-d_6) δ: 160.2, 154.7, 153.4, 139.6, 138.8, 128.9, 128.6, 128.5, 128.0, 127.1, 125.1, 122.8, 120.0, 119.9, 108.9, 103.0, 100.8, 41.4, 31.1, 20.3, 13.8. LC-MS: m/z = 317 (M + H), positive mode; Anal. Calcd for molecular formula $C_{21}H_{20}N_2O$; C, 79.72; H, 6.37; N, 8.85%; found: C, 79.61; H, 6.31; N, 8.79%.

General procedure for the one-pot synthesis of pyrimido-[4,5-*b*] & [5,4-*b*]indoles (Method A):. An oven dried Ace Pressure tube with a Teflon stir bar was charged with $Pd_2(dba)_3$ (1.3 mg, 1.4 µmol, 1.0 mol% Pd), BINAP (0.18 mg, 2.9 µmol, 1.5 mol%), amide (86 mg, 0.07 mmol), base [Cs_2CO_3 (195 mg) or K_3PO_4 (127 mg) or K_2CO_3 (83 mg) or *t*-BuOK (58 mg)], 3-halo-2-formylindoles or 2-halo-3-carbonylindoles (0.2 g, 5.9 µmol) and *t*-BuOH (2.0 mL) and then capped with a Teflon screw cap and the mixture was heated to 110 °C with stirring and the reaction was monitored by TLC. When the starting material was completely consumed, the reaction mixture was cooled to <80 °C and $HCOONH_4$ (6.0 equiv) in *t*-BuOH (2 mL) was added in one portion. The resulting mixture was heated back to 110 °C and the reaction mixture was stirred for the according time mentioned in Table 4. When the reaction was complete, the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and the resulting solution was filtered through celite, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate) to give the corresponding pyrimido[4,5-*b*] and [5,4-*b*]indole product.

General procedure for the one-pot synthesis of pyrimido-[4,5-*b*] & [5,4-*b*]indoles (Method B). An oven dried Ace Pressure tube with a Teflon stir bar was charged with either *N*-(3-carbonyl-1-(substituted)-1*H*-indol-2-yl)amides or *N*-(1-(substituted)-2-formyl-1*H*-indol-3-yl)amides (1.0 equiv) and $HCOONH_4$ (6.0 equiv) in *t*-BuOH (6 mL). The pressure tube was then sealed with a Teflon screw-cap and the reaction was placed in a pre-heated oil bath at 110 °C. The reaction mixture was stirred for according time mentioned in Table 4 and then removed from the oil bath and allowed to cool to room temperature. The reaction mixture was then diluted with ethyl acetate. The resultant reaction mixture was extracted with EtOAc (20 mL), washed with water (100 mL) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to obtain the pure product (**3a–3t**). Hexane was added and removed twice more before the product was dried *in vacuo*.

4-Methyl-2-(thiophen-2-yl)-9*H*-pyrimido[4,5-*b*]indole (3a). Yellow solid; m.p. 127–129 °C; IR (KBr): 3050, 2856, 1919, 1852, 1680, 1570, 1462, 1252, 1170, 1100, 1028, 990, 752 cm^{-1}. ^{1}H NMR (400 MHz, TMS, $CDCl_3$) δ: 11.0 (s, 1H,), 7.89–7.88 (m, 1H), 7.78–7.70 (m, 1H), 7.69–7.29 (m, 3H), 7.24–7.21 (m, 2H,), 2.73 (s, 3H). ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ: 161.8, 158.4, 144.4, 137.2, 133.0, 132.3, 130.7, 128.4, 123.7, 122.7, 122.3, 119.3, 111.8, 101.0, 29.9; LC-MS: m/z = 265 (M + H), positive mode; Anal. Calcd for molecular formula $C_{15}H_{11}N_3S$; C, 67.90; H, 4.18; N, 15.84%; found: C, 67.81; H, 4.23; N. 15.76%.

9-Butyl-2,4-dimethyl-9*H*-pyrimido[4,5-b]indole (3b). Pale purple or pink solid; m.p. 117–119 °C; IR (KBr): 3059, 2926, 2856, 1923, 1886, 1682, 1622, 1574, 1494, 1469, 1408, 1255, 1174, 1111, 1028, 999, 927, 794, 736 cm^{-1}. ^{1}H NMR (400 MHz, TMS, $CDCl_3$) δ: 8.07 (d, 1H, J = 8.0 Hz), 7.53–7.50 (m, 2H), 7.35–7.26 (m, 1H), 4.43 (t, 2H, J = 8.0 Hz), 2.95 (s, 3H), 2.82 (s, 3H), 1.89–1.85 (m, 2H), 1.41–1.35 (m, 2H), 0.96 (t, 3H, J = 8.0 Hz). ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ: 163.7, 159.2, 155.8, 139.0, 126.3, 122.5, 120.9, 120.2, 109.7, 109.5, 41.1, 30.8, 29.7, 26.4, 20.2, 13.7. LC-MS: m/z = 254 (M + H), positive mode; Anal. Calcd for molecular formula $C_{16}H_{19}N_3$; C, 75.85; H, 7.56; N, 16.59%; found: C, 75.96; H, 7.52; N, 16.51%.

9-Ethyl-2-phenyl-9*H*-pyrimido[4,5-*b*]indole (3k). Greenish brown solid; m.p. 114–116 °C, IR (KBr): 3061, 2978, 2930, 1668, 1622, 1581, 1556, 1493, 1467, 1433, 1400, 1359, 1224, 1140, 1091, 1066, 1024, 993, 923, 810, 769, 738, 698, 543, 449, 405 cm^{-1}. ^{1}H NMR (400 MHz, TMS, $CDCl_3$) δ: 9.33 (s, 1H), 8.65 (m, 2H), 8.13 (d, 1H, J = 7.8 Hz), 7.58–7.50 (m, 5H), 7.39–7.35 (m, 1H), 4.59 (q, 2H, J = 7.2 Hz), 1.54 (t, 3H, J = 7.24 Hz). ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ: 160.8, 155.4, 148.0, 139.5, 138.7, 132.0, 130.1, 129.2, 128.4, 128.3, 127.3, 121.4, 121.1, 119.5, 112.5, 109.6, 36.2, 13.9. LC-MS: m/z = 275 (M + H), positive mode; Anal. Calcd for molecular formula $C_{18}H_{15}N_3$; C, 79.10; H, 5.53; N, 15.53%; found: C, 79.21; H, 5.58; N, 15.58%.

9-Ethyl-2-(pyridin-3-yl)-9*H*-pyrimido[4,5-*b*]indole (3l). Yellowish orange solid; m.p. 92–94 °C; IR (KBr): 3042, 2935, 2920, 1610, 1562, 1552, 1530, 1485, 1475, 1390, 1200, 1132, 1085, 850, 795, 732, 709, 415 cm^{-1}. ^{1}H NMR (400 MHz, TMS, $CDCl_3$) δ: 9.79 (s, 1H), 9.27 (d, 1H, J = 2.0 Hz), 8.81 (d, 1H, J = 7.84 Hz), 8.68 (s, 1H), 8.08 (d, 1H, J = 7.64 Hz), 7.54 (d, 1H, J = 7.32 Hz), 7.49–7.47 (m, 1H), 7.42–7.39 (m, 1H), 7.36–7.32 (m, 1H), 4.53 (q, 2H, J = 4.0 Hz), 1.50 (t, 3H, J = 8.0 Hz). ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ: 158.6, 155.1, 149.9, 147.9, 139.5, 135.5, 134.1, 132.8, 123.3, 121.5, 121.3, 119.2, 113.0, 109.7, 108.2, 36.3, 13.9. LC-MS: m/z = 275 (M + H), positive mode; Anal. Calcd for molecular formula $C_{17}H_{14}N_4$; C, 74.43; H, 5.14; N, 20.42%; found: C, 74.32; H, 5.21; N, 20.36%.

General procedure for the synthesis of dihydropyrido[4,5-*b*]-indoles. A round bottom flask with a Teflon stir bar was charged with *N*-(3-formyl-1-(substituted)-1*H*-indol-2-yl)amides (1.0 mmol),

nitro styrene (1.0 mmol) and DABCO (0.5 mmol) and the mixture was stirred and heated at 70 °C for 3 h. After the reaction was over, the residue was diluted with dichloromethane, adsorbed on silica gel and subjected to column chromatography to obtain **4a–b** in good yields.

(9-Ethyl-3-nitro-2-phenyl-2,9-dihydro-1*H*-pyrido[2,3-*b*]indol-1-yl)(phenyl)methanone (4a). Pale yellow solid; m.p. 232–234 °C; IR (KBr): 3063, 2926, 2854, 1670, 1612, 1508, 1464, 1352, 1269, 1095, 1018, 750, 690 cm^{-1}. ^1H NMR (400 MHz, TMS, $CDCl_3$) δ: 8.61 (s, 1H), 7.76–7.74 (m, 1H), 7.53–7.52 (m, 4H), 7.40–7.35 (m, 4H), 7.32–7.19 (m, 5H), 7.16 (s, 1H), 3.63 (q, 2H, J = 4.0 Hz), 0.91 (t, 3H, J = 7.32 Hz). ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ: 169.7, 149.3, 139.6, 137.1, 136.4, 135.8, 133.1, 132.1, 128.9, 128.8, 128.7, 128.5, 127.1, 126.9, 126.6, 124.0, 123.4, 122.7, 118.6, 117.2, 112.4, 111.0, 102.1, 58.3, 39.6, 13.6. LC-MS: m/z = 424 (M + H), positive mode; Anal. Calcd for molecular formula $C_{26}H_{21}N_3O_3$; C, 73.74; H, 5.00; N, 9.92%; found: C, 73.65; H, 5.00; N, 9.98%.

(9-Ethyl-3-nitro-2-phenyl-2,9-dihydro-1*H*-pyrido[2,3-*b*]indol-1-yl)(thiophen-2-yl)methanone (4b). Orange solid; m.p. 217–219 °C; IR (KBr): 2916, 1651, 1612, 1527, 1509, 1432, 1272, 1105, 1018 cm^{-1}. ^1H NMR (400 MHz, TMS, $CDCl_3$) δ: 8.60 (s, 1H), 7.75–7.74 (m, 1H), 7.58–7.57 (m, 1H), 7.38–7.37 (m, 1H), 7.32–7.30 (m, 2H), 7.29–7.26 (m, 6H), 7.25–7.05 (m, 1H), 6.95–6.93 (m, 1H), 3.69 (q, 2H, J = 4.0 Hz), 0.87 (t, 3H, J = 4.0 Hz). ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ: 162.7, 138.6, 137.4, 136.2, 135.8, 135.7, 135.5, 133.4, 133.3, 132.6, 128.8, 127.8, 127.1, 126.7, 126.4, 123.9, 123.6, 122.7, 118.7, 111.0, 102.5, 58.3, 39.5, 13.6. LC-MS: m/z = 428 (M − H), negative mode; Anal. Calcd for molecular formula $C_{24}H_{19}N_3O_3S$; C, 67.12; H, 4.46; N, 9.78%; found: C, 67.26; H, 4.51; N, 9.65%.

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